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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 52004

Application Number: 09/318,870
Filing Date: May 26, 1999
Appellant(s): SEGAL, ANDREW H.

Kathleen M. Williams
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 02 2004

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the Brief.

(2) Related Appeals and Interferences

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

Absent of good and sufficient reasons why the Rule 132 Declaration by Dr. Segal filed with the Amendment After Final Rejection filed on 03/25/04 ("second " Segal Declaration) was not earlier presented, said Declaration was not considered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's Brief includes a statement that claims do not stand or fall together with regards to rejection under 35 U.S.C. 112, first paragraph, 35 U.S.C. 102(e), or 35 U.S.C. 103 (a) and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

At pages 3 and 4 of the Brief, Appellant asserts that the claims under appeal may be grouped as : Group I: Claims 1, 3-8, 17-20, and 22-25; Group II : Claim 2 and 3-8; Group III : Claim 13 and 14; Group IV: Claim 15 and 16; Group V: Claim 21. Appellant submits that the claims of each group are separately patentable over the claims of the other groups as the independent claim of each group contains elements which render the claims of each group novel and patentably distinct over the other groups and because the claims of each group contain structurally distinct cytokines. Moreover, the claims of each group do not stand or fall together as each claim contains elements not present in the other members of the group.

The appellant's statement in the brief that claims 1-8,13, 14,17-20 and 22-25 do not stand or fall together under enablement rejection 35 U.S.C. 112 first paragraph is not agreed with because contrary to Appellant's assertion the enablement rejection under 35 U.S.C. 112, first paragraph stands with regard to a method of vaccinating a mammal to a selected antigen. Claims 1-8,13, 14,17-20 and 22-25 present definitions of the same scope and should stand or fall together with respect to issues of enablement.

The appellant's statement in the brief that claims 1,2, 13,14,17-19 and 22-25 do not stand or fall together under rejection 35 U.S.C. 102(e) is not agreed with because contrary to Appellant's assertion claims 1,2, 13,14,17-19 and 22-25 defines similar embodiment and should stand or fall together with respect to art rejection under 35 U.S.C. 102(e).

The appellant's statement in the brief that claims 3-8 and 20 do not stand or fall together under rejection 35 U.S.C. 103(a) is not agreed with because contrary to Appellant's assertion claims 3-8 and 20 defines similar embodiment and should stand or fall together with respect to art rejection under 35 U.S.C. 103(a).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

1. US Patent 6,277,368.

2. US Patent 6,248,329.

3. Immunobiology, Third Edition, Chapter 13, Eds. C. Janeway; P.et al., 1990, Garland Publishing, New York, NY.

4. Ellis, R.W. Chapter 29 of "VACCINES" Eds. Plotkin, S.A. et al. 1988, W. B. Saunders Philadelphia, PA.

5. Spitler et al., Cancer Biotherapy, 1995, Vol.10, pages 1-3.

6. Ezzell C. et al., NIH Research, 1995, Vol.7, pages 46-49.

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Issue 1: Enablement/35 U.S.C. 112, first paragraph

Claims 1-8, 13, 14, 17-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least 20 % increasing in a survival period of vaccinated mice compare to control non-vaccinated mice during B16 cells –initiated melanoma tumor formation comprising vaccinated mice with composition comprising cytokine-coated B16 cells, does not reasonably provide enablement for a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The specification only discloses that mice vaccinated with cytokine-coated melanoma B16 cells will have a considerably longer survival period as compare to control mice (see examples 7-9 in particular).

The claims are drawn to a method of vaccinating a mammals. By definition, a vaccine is a composition to induce a specific immunity that **prevent** or protect against a specific disease caused by a specific agent. One of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of antigen - specific antibody. The second criterion for a vaccine is the ability to stimulate memory T lymphocytes (cell-mediated immune response) (See

Immunobiology, Third Edition, Chapter 13 in particular). The specification provides no information on the immunogenicity of *any* vaccine comprising *any* cytokine-coated cell comprising antigen or the ability of such to protect or prevent from antigen-specific disease. Moreover, Applicant acknowledges that tumors were detected in mice vaccinated with composition comprising cytokine-coated B16 cells (see page 101, line 16-20 in particular). The specification fails to teach that the vaccine comprising *any* cytokine-coated cell comprising antigen are capable of generating an antibody response. The specification also fails to teach that the antibody response to the claimed *any* cytokine-coated cell comprising antigen thereof, provides for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". Moreover, Chandrasheker et al., (US Patent 6,248,329) teach that although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from specific disease, associated with said antigen (see column 1, lines 35-45 in particular). In addition, Spitler , (Cancer Biotherapy, 1995, v.10 pages 1-3 teaches that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response" (see page 1, column 1, paragraph 1 in particular). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (NIH Research, 1995, Vol.7, pages 46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see entire document, particularly the last paragraph). It is

well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

The specification fails to teach that claimed *any* cytokine-coated cell comprising antigen does in fact confer protection from infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to teach that the claimed *any* cytokine-coated cell comprising antigen is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize *any* cytokine-coated cell comprising antigen as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen exemplified in the specification.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the

limited amount of direction provided given the breadth of the claims, it would take undue trial and error experimentation to practice the claimed invention.

Issue II: Rejected under 35 U.S.C. 102 (e)

Claims 1, 2, 13, 14, 17-19, 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Hiserodt et al. (US Patent 6,277,368).

US Patent '368 teaches a method of vaccinating a mammal, including mouse , to selected antigen, comprising administering a vaccine comprising a primary tumor cells and cytokine-secreting cells (see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cells that already express an antigen, a tumor cell antigen for example, with engineered cytokines that can become membrane-bound (see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular). US Patent '368 teaches that cytokine is a GM-CSF, that is a ligand for GM-CSF receptor (see column 7, lines 31, or column 10, lines 52-65 in particular). US Patent '368 teaches that said cytokines can be membrane-bound capable of potentiating an immunological response against the tumor-associated antigen (column 15, lines 36-45 in particular). US Patent '368 teaches a immunogenic composition comprising 2 population of cells: first population is tumor cells i.e. specific antigen expressing cells and second population is the cytokine-producing cells (see column 15, line 35-40 and claim 9 in particular). Cytokines secreted by said second cytokine-secreting cells would be exogenous cytokines that are produced outside of first population of antigen expressing cells, that will become "cytokine-coated cells", wherein said cytokine of said cytokine-coated cells is exogenous to said antigen expressing cell. Moreover, US Patent '368 teaches that it is preferable that cytokine attached to the cell membrane to keep it in the vicinity of bystander tumor antigen comprised in the vaccine (see column 16, lines 28-35 in particular). US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity (see column 16, line 50-

65 in particular). US Patent '368 teaches that said vaccine composition can be attenuated (see overlapping columns 23 and 24 in particular).

Claims 22 and 25 are included because the claimed functional limitation would be inherent properties of the referenced method , because it is clear that both the prior art and claimed invention administer the same treatment to achieve the same results using the same extremely bioactive, natively bioactive or suprabioactive cytokines and cytokine-coated cells that would be unable to divide in vitro . Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. Since the office does not have a laboratory to test the reference cytokines it is applicant's burden to show that the reference cytokines do not have the same functional limitation as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teaching anticipates the claimed invention.

Issue III: Rejected under 35 U.S.C. 103 (a)

Claims 3-8 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiserodt et al. (US Patent 6,277,368) in view of the known fact disclosed in the Specification on pages 52-54.

The teaching of US Patent '368 has been discussed, supra. US Patent '368 teaches that cytokines can be engineered to become stably associated with the plasma membrane (see column 16, lines 50-65 in particular). US Patent '368 does not teach specific types of engineered cytokine or specific opsonin-enhanced cells as recited in claims 3-8 and 20.

The Known fact disclosed in the Specification on pages 52-54 and 66 – 68 teaches that it is conventional and within the skill of the art to produce : (i) an opsonin-enhanced cells, wherein opsonin of said cells is mannose binding protein or alpha chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching the lipid , e.g. a long -chain fatty acid, for example palmitate or GPI moiety to said cytokine to permit a complex to become stably associated with plasma membrane.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 to those of US Patent '368 to obtain a claimed method of vaccinating a mammal to a selected antigen, comprising administering said vaccine composition comprising an opsonin-enhanced cells and engineered cytokine comprising a lipid or GPI moiety or palmitate.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because at the time the invention was made it would be conventional and within the skill of the art to produced a membrane-bound form of cytokine wherein a specific modification , i.e. engineered cytokine wherein lipid , e.g. a long-chain fatty acid, for example palmitate or GPI moiety is attached to said cytokine and to produced an opsonin-enhanced cells that will allows more efficient binding, of said engineered cytokine into said cell as taught by the known fact disclosed in the Specification on pages 52-54 and 66-68. The advantage of using said membrane-bound form of cytokine in a method of vaccinating a mammal is taught by US Patent'368. In addition, US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Responding to Argument

Issue 1: Enablement/35 U.S.C. 112, first paragraph

Claims 1-8, 13, 14, 17-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least a 20 % increase in the survival period of vaccinated mice compare to control non-vaccinated mice during B16 cells –initiated melanoma tumor formation comprising vaccinated mice with composition comprising cytokine-coated B16 cells, does not reasonably provide enablement for a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

At page 5 of the Brief, Appellant argues that the term "vaccinate" is define in the specification as the "modulation of an immune response to an antigen. More specifically, the specification teaches that if at least 10% of the animals in the test group survive 100 % longer than the mean survival in the control group, the test is positive. At page 6 of the Brief, Appellant submits that the Examiner's definition of the term "vaccinate" is inconsistent with Appellant's specification –defined definition and further asserts that the law expressly gives Appellant the ability to define terms in the claims according to Appellant's wishes. At page 7 of the Brief, Appellant submits that the Declaration under 37 C.F.R.1.132 by Dr. Andrew Segal, filed on 02/28/03 (the first Segal declaration) provides data to show that the vaccine composition of the present invention are effective in vaccinating a mammal to which they are administered

The examiner acknowledges that while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). However, during examination, claims are to be interpreted as broadly as their term reasonably allow because ambiguity and undue breadth of the language can be readily corrected to fashion a claim which is precise, clear, correct and unambiguous. *In re Zletz*, 13 USPQ2d 1320 (Fed.Cir. 1989). The specification only discloses that mice vaccinated with cytokine-coated melanoma B16 cells will have a considerably longer survival period as compare to control mice. For example, Example 7 teaches that after administering of cytokine-coated (GM-CSF-GPI-coated) B16 cell only 20 % of the mice in tested group has a survival time which was greater than the mean survival of the control group (see examples 7-9 in particular). Similarly, the Declaration under 37 C.F.R.1.132 by Dr. Andrew Segal (first Sedal declaration) provides only data demonstrating the ability GM-CSF-coated CMS-5 fibrosarcoma cells to increase a survival period of vaccinated mice compared to control non-vaccinated mice during CSM-5 –initiated fibrosarcoma tumor formation. Moreover, Applicant acknowledges that tumors were detected in mice vaccinated with composition comprising cytokine-coated B16 cells (see page 101, line 16-20 in particular). One of the skill in the art at the time the invention was made would clearly interpreted these data as *increasing in a survival period of treated mice, not completely prevention of development of tumors.* Moreover, the current state of the art is that there is a lack in effective "cancer vaccines" as taught by Spitler.

At page 13 of the Brief, Appellant argues that the specification teaches on pages 16-47 more than six different families of cytokines useful in the invention, including over 80 specifically referenced cytokine molecules which may be used in vaccine composition of the invention. Appellant further argues that the specification teaches at pages 68-71 that antigen useful in the method of invention include viral antigens, bacterial antigens , fungal antigens, parasite antigens and tumor antigens. At page 16 of the Brief, Appellant argues that that the specification teaches method for determining whether an animal has been vaccinated by a vaccine composition according to the invention. Thus

one skilled in the art may have to test a specific vaccine composition to determine whether it provides the particular vaccination desired.

Contrary to Appellant's assertions , the issue of the rejection was not about different cytokines that can be used in vaccine composition comprising cytokine-coated cells. The issue was that one of the criteria for a vaccine is the levels of antibody (humoral immune response) before and after immunization and the success of vaccination is judged by the extent of increase in the level of antigen - specific antibody. The second criterion for a vaccine is the ability to stimulate memory T lymphocytes (cell-mediated immune response) (See Immunobiology, Third Edition, Chapter 13 in particular). The specification provides no information on the immunogenicity of *any* vaccine comprising *any* cytokine-coated cell comprising antigen or the ability of such to protect or prevent from antigen-specific disease. The specification fails to teach that the vaccine comprising *any* cytokine-coated cell comprising antigen are capable of generating an antibody response. The specification also fails to teach that the antibody response to the claimed *any* cytokine-coated cell comprising antigen thereof, provides for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". Moreover, Chandrasheker et al., (US Patent 6,248,329) teach that although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessary correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from specific disease, associated with said antigen (see column 1, lines 35-45 in particular). In addition, Spitler , (Cancer Biotherapy, 1995, v.10 pages 1-3 teaches that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work".

Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response" (see page 1, column 1, paragraph 1 in particular). The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (NIH Research, 1995, Vol.7, pages 46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

The specification fails to teach that claimed *any* cytokine-coated cell comprising antigen does in fact confer protection from infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to teach that the claimed *any* cytokine-coated cell comprising antigen is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize *any* cytokine-coated cell comprising antigen as operative vaccines. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine-coated cell comprising said antigen exemplified in the specification.

Issue II: Rejected under 35 U.S.C. 102 (e)

Claims 1, 2, 13, 14, 17-19, 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Hiserodt et al. (US Patent 6,277,368).

At page 21 of the Brief, Appellant argues that while in one embodiment US Patent '368 teaches an antigen bearing cell in combination with exogenous cytokine, the exogenous cytokine is secreted by another cell and is thus not associated with the cell surface of the antigen bearing cell to yield a cytokine coated cell as claimed. Appellant further states that US Patent '368 teaches only endogenous membrane bound cytokine and does not teach a cell bearing an exogenous membrane bound cytokine.

It is noted that endogenous cytokines of cytokine-coated cell taught by US Patent '368 and exogenous cytokine of cytokine-coated cell of the instant application are structurally the same cytokines that inherently have the same properties. The only difference is that "exogenous" cytokine is introduced from or produced outside the cell. The term " exogenous" carries little patentable weight in the absence of evidence of structural difference. Thus it is clear that both the prior art and the claimed method administered the same treatment i.e. cytokine coated cells to the same patient i.e. mammals to achieve the same result, i.e. to induced an immune response. The patentability of the method of vaccinating a mammal comprising administering a cytokine-coated cell does not depend on source of cytokine to produce a cytokine-coated cells in the absence of evidence of structural difference . Moreover, it is noted that both the instant specification and US Patent '368 clearly teaches the advantages of using a membrane-bound cytokines over soluble cytokines to increase an immune response to an antigen comprises by the cell.(see page 15 and column 16 respectively).

US Patent '368 teaches a method of vaccinating a mammal, including mouse , to selected antigen, comprising administering a vaccines comprising a primary tumor cells and cytokine-secreting cells (see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cell that already express an antigen, a tumor cell antigen for example, with engineered cytokines that can become membrane-bound (see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular). US Patent '368 teaches that cytokine is a GM-CSF, that is a ligand for GM-CSF receptor (see column 7, lines 31, or column 10, lines 52-65 in particular). US Patent '368 teaches that said cytokines can be membrane-bound capable of potentiating an immunological response against the tumor-associated antigen (column 15, lines 36-45 in particular). US Patent '368 teaches that membrane-associated form of cytokine creates a bridge between cytokine-coated cell and responding lymphocytes to to increase an immune response to an antigen comprises by the cell (see column 16, lines 30-60 in particular). US Patent '368 teaches a immunogenic composition comprising 2 population of cells: first population is tumor cells i.e. specific antigen expressing cells and second population is the cytokine-producing cells (see column 15, line 35-40 and claim 9 in particular). Cytokines secreted by said second cytokine-secreting cells would be exogenous cytokines that are produced outside of first population of antigen expressing cells, that will become "cytokine-coated cells", wherein said cytokine of said cytokine-coated cells is exogenous to said antigen expressing cell. Moreover, US Patent '368 teaches that it is preferable that cytokine attached to the cell membrane to keep it in the vicinity of bystander tumor antigen comprised in the vaccine (see column 16, lines 28-35 in particular). US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity (see column 16, line 50-65 in particular). US Patent '368 teaches that said vaccine composition can be attenuated (see overlapping columns 23 and 24 in particular).

Claims 22 and 25 are included because the claimed functional limitation would be inherent properties of the referenced method , because it is clear that both the prior art and claimed

invention administer the same treatment to achieve the same results using the same extremely bioactive, natively bioactive or suprabioactive cytokines and cytokine-coated cells that would be unable to divide in vitro . Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. Since the office does not have a laboratory to test the reference cytokines it is applicant's burden to show that the reference cytokines do not have the same functional limitation as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teaching anticipates the claimed invention.

Issue III: Rejected under 35 U.S.C. 103 (a)

Claims 3-8 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hiserodt et al. (US Patent 6,277,368) in view of the Known fact disclosed in the Specification on pages 52-54.

At page 22 of the Brief, Appellant asserts that US Patent '368 teachings are deficient with respect the specific types of engineered cytokine or specific opsonin-enhanced cells. Appellant further submits that the "known fact" only asserts that the technology existed to link a lipid moiety to a cytokine molecule or to employ an opsonin to enhance binding and engulfment but does not teaches that such a modification is obvious for the purposes of immunizing an animal. At page 24 of the Brief, Appellant asserts that it would not been obvious to combine, for purposes of immunization, an opsonin with the cytokine-coated cells of the invention, because immunization with cytokine coated cells had never been described outside of the present application.

Appellant have traversed the primary references pointing to the differences between the claims and the disclosure in each reference. Appellant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This Appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

The Examiner disagrees with Appellant's statement that "immunization with cytokine coated cells had never been described outside of the present application". As has been discussed in Section 10, Issue II above, it is the Examiner position that US Patent '368 teaches immunization with cytokine-coated cells. Moreover, Appellant acknowledge that US Patent '368 teaches immunization with endogenous cytokine-coated cells (see page 21 of the Brief in particular). US Patent '368 teaches that cytokines can be engineered to become stable associated with the plasma membrane. Moreover, US Patent '368 explicitly teaches the advantage of using a membrane-bound form of cytokine compare to soluble form. US Patent '368 further teaches that when a particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to create a membrane-bound form (see column 16, lines 30-65 in particular).

US Patent '368 does not teach specific types of engineered cytokine or specific opsonin-enhanced cells as recited in claims 3-8 and 20.

The Known fact disclosed in the Specification on pages 52-54 and 66 – 68 teaches that it is conventional and within the skill of the art to produce : (i) an opsonin-enhanced cells, wherein

opsonin of said cells is mannose binding protein or alph' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching the lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety to said cytokine to permit a complex to become stable associated with plasma membrane. In other words , at the time the invention was made one skill in the art would know that to produced membrane-bound form of cytokine said specific modifications should be used. Moreover, Appellant acknowledge that said technologies existed at the time the invention was made (see page 22 of the Brief in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 to those of US Patent '368 to obtain a claimed method of vaccinating a mammal to a selected antigen, comprising administering vaccine composition comprising an opsonin-enhanced cells and engineered cytokine comprising a lipid or GPI moiety or palmitate.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because at the time the invention was made it would be conventional and within the skill of the art to produced a membrane-bound form of cytokine wherein a specific modification , i.e. engineered cytokine wherein lipid , e.g. a long-chain fatty acid, for example palmitate or GPI moiety is attached to said cytokine and to produced an opsonin-enhanced cells that will allows more efficient binding, of said engineered cytokine into said cell as taught by the known fact disclosed in the Specification on pages 52-54 and 66-68. The advantage of using said membrane-bound form of cytokine in a method of vaccinating a mammal is taught by US Patent'368. In addition, US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms with a high degree of lipophyllicity.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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